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PATENT
Docket No. 01723326

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent Application of:	Jeffrey Owen Phillips	
Serial No.:	09/481,207	Examiner: Fan, J.
Filed:	January 11, 2000	Group Art Unit: 1625
For:	Novel Substituted Benzimidazole Dosage Forms and Method of Using Same	

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TO THE ASSISTANT COMMISSIONER OF PATENTS,
SIR:

DECLARATION OF JOSEPH B. SCHWARTZ UNDER 37 C.F.R. §1.132

I, Joseph B. Schwartz, Ph.D., declare and state as follows:

1. I received a Ph.D. in Pharmaceutical Chemistry from The University of Michigan in December 1967. My dissertation was entitled "Drug Release from Inert Wax Matrices."

2. I am employed as a Professor of Pharmaceutics and am the Director of Industrial Pharmacy Research at the Philadelphia College of Pharmacy, a college of the University of the Sciences in Philadelphia, a nonprofit Pennsylvania corporation, in Philadelphia, Pennsylvania. In my role as a Professor of Pharmaceutics I teach the course in Industrial Pharmacy, which encompasses, among other things, formulation theory for oral dosage forms, unit operations, etc. In my role as Director of Industrial Pharmacy Research I serve as the coordinator of the Contract Research and Contract Development effort of the Pharmaceutics Group/Faculty in the Department of Pharmaceutical Sciences. I have had 13 years industrial experience (and another 20 years at the College) in the design and formulation of dosage forms for human use. I have served on the U.S. Food and Drug Administration (FDA) Advisory Committee for Generic

Drugs (renamed the Advisory Committee for Pharmaceutical Science). In addition to my teaching at PCP, I have also served as an Instructor at the FDA and at pharmaceutical companies. I served as the Editor for the PDA Journal from 1988 to 2000. My Curriculum Vitae is attached to this Declaration as Exhibit A and is expressly incorporated by reference in this Declaration.

3. Under my direction, the timed acid neutralization of a representative amount of calcium carbonate, sodium bicarbonate, and combinations of the two, were evaluated. Specifically the acid neutralization effect of these compounds was evaluated in the "Kinetic Acid Neutralization Model." Briefly, the Model entails the use of a glass flask (in the form of a 200 mL dissolution flask) to hold the 0.1 N hydrochloric acid (HCl) (to simulate the acidity of the stomach in the fasted state). Fifty mL is considered the volume of acid usually found in a fasted stomach, but for experimental convenience, our model utilized 100 mL (double the usual fasted stomach volume). An overhead stirrer maintained at a constant, controlled and reproducible rpm, stirred the contents in the flask. It is believed that the human stomach adds HCl to the stomach contents at the rate of 30 mL per hour. The Kinetic Model added, by a peristaltic pump (Watson/Marlow Multichannel PumpPro model with acid resistant tubing), 200 mL per hour of 0.05 N HCl. This rate compensates for the doubling of the initial volume of 0.1 N HCl from 50 to 100 mL. To simulate stomach emptying, fluid was withdrawn from the flask at the same rate and by the same peristaltic pump, maintaining the 100 mL volume constant. This New test method combines the concepts of USP<301>, Acid-Neutralizing Capacity Test, and the concepts of USP <724>, the Flow Through Cell for Drug Release Testing. The calcium carbonate used in the study was commercially available powder from Whittaker, Clark & Daniels, Inc., Lot No. A0169-12. The sodium bicarbonate used in the study was commercially available powder from Church & Dwight Co., Inc., Lot No. 1054F.

4. In the study, the pH of the initial acid in the flask was measured as a function of time. At time zero, the antacid or antacid combination was added to the flask, and the pH of the contents measured, starting at one minute intervals, and progressing at convenient time intervals until the pH fell to a value of 3 or less.

5. For the analysis of pH, an Orion pH Meter (model 720A) equipped with an Orion pH electrode (combination probe/PerpHeot Ross Semimicro Electrode) was employed.

Should compare with art of 224, 225.

6. Table No. 1 illustrates the data measured for the effect of a single dose of calcium carbonate or sodium bicarbonate treatment on neutralization of acid as a function of time.

40 mg PPI.
16 mg $CaCO_3$

TABLE NO. 1

30 mEq Calcium Carbonate		16 mEq Calcium Carbonate		9.5 mEq Sodium Bicarbonate		20 mEq Sodium Bicarbonate	
Time (min)	pH	Time (min)	pH	Time (min)	pH	Time (min)	pH
1	5.73	1	5.67	1	6.57	1	6.99
2	5.73	2	5.66	2	6.57	2	6.99
3	5.71	3	5.66	4	6.56	3	6.99
4	5.71	4	5.66	5	6.56	4	6.98
5	5.71	5	5.65	12	6.46	5	6.98
12	5.71	12	5.64	15	6.46	12	6.89
15	5.7	15	5.63	17	6.41	15	6.89
20	5.69	20	5.6	27	6.13	25	6.85
25	5.67	25	5.56	31	5.95	36	6.68
35	5.64	32	5.43	36	5.6	39	6.63
41	5.6	35	5.31	42	2.69	43	6.55
45	5.58	40	3.14	43	2.47	54	6.24
52	5.5	45	1.89	44	2.32	57	6.13
55	5.41	50	1.56	45	2.2	61	5.91
59	5.01	55	1.42	52	1.84	64	5.64
61	3.95	60	1.31			65	5.6
62	3.25					67	5.06
63	2.77					68	4.05
64	2.42					69	2.82
						70	2.51
						71	2.33
						73	2.12

Data was also measured for a single dose of a combination of calcium carbonate and sodium bicarbonate. The results of these combination studies are summarized in Table Nos. 3 and 4 below.

7. The summary of Table No. 2 shows a comparison of the results generated from Table No. 1:

TABLE NO. 2

	30 mEq Calcium Carbonate	**16 mEq Calcium Carbonate**	**9.5 mEq Sodium Bicarbonate**	**20 mEq Sodium Bicarbonate**
Maximum pH	5.73	5.67	6.57	6.99
Time Max pH achieved	1 minute	1 minute	1 minute	1 minute
Time above pH 5	59 minutes	37 minutes	38 minutes	68 minutes
Time above pH 5.5	52 minutes	27 minutes	37 minutes	65 minutes
Time above pH 6	0 minutes	0 minute	29 minutes	59 minutes

8. Table No. 3 shows a summary of the results generated for a single 10 mEq dose of a combination of calcium carbonate and sodium bicarbonate on neutralization of acid as a function of time:

TABLE NO. 3

	10 mEq 75% Sodium Bicarbonate 25% Calcium Carbonate	**10 mEq 50% Sodium Bicarbonate 50% Calcium Carbonate**	**10 mEq 25% Sodium Bicarbonate 75% Calcium Carbonate**
Maximum pH	6.3	5.91	5.63
Time Max pH achieved	1 minute	1 minute	1 minute
Time above pH 5	27 minutes	18 minutes	26 minutes

Time above pH 5.5	25 minutes	16 minutes	22 minutes
Time above pH 6	14 minutes	0 minute	0 minutes

9. Table No. 4 shows a summary of the results generated for a single 20 mEq dose of a combination of calcium carbonate and sodium bicarbonate on neutralization of acid as a function of time:

TABLE NO. 4

	20 mEq 75% Sodium Bicarbonate 25% Calcium Carbonate	**20 mEq 50% Sodium Bicarbonate 50% Calcium Carbonate**	**20 mEq 25% Sodium Bicarbonate 75% Calcium Carbonate**
Maximum pH	6.73	6.43	6.04
Time Max pH achieved	1 minute	1 minute	1 minute
Time above pH 5	58 minutes	56 minutes	53 minutes
Time above pH 5.5	55 minutes	52 minutes	47 minutes
Time above pH 6	47 minutes	33 minute	2 minutes

10. Based on my experience and training, I believe that the "Kinetic Acid Neutralization Model" and test protocol described above encompasses an *in vitro* representation of what is believed to be the mechanism of antacid neutralization in the body. We used an amount of acid that is two times the "normal" physiological amount, and added replacement acid at two times the amount considered the normal influx of HCl to the fasting stomach, and emptied the flask at two times the normal physiological rate of stomach emptying of liquids. The dose milliequivalent antacid doses were selected on the basis of 50 mL acid in the stomach, and we therefore doubled the dose of antacid.

11. I would expect significantly less acid degradation of the proton pump inhibitor when 20 milliequivalents (mEq) of sodium bicarbonate or 30 mEq of calcium carbonate is used

versus 9.5 mEq of sodium bicarbonate or 16 mEq of calcium carbonate. This is because the greater amount of buffer results in a higher pH of the test solution in the Model over a longer period of time. For example, 20 mEq of sodium bicarbonate maintains the pH of the test solution greater than 5.5 for 68 minutes, as compared to 9.5 mEq of sodium bicarbonate, which maintains a pH of greater than 5.5 for only 37 minutes. Similarly, 30 mEq of calcium carbonate maintains the pH of the test solution greater than 5.5 for 52 minutes, while 16 mEq of calcium carbonate maintains the pH of the test solution of greater than 5.5 for only 27 minutes.

12. I would also expect significantly less acid degradation of the proton pump inhibitor when 20 mEq of a combination of sodium bicarbonate and calcium carbonate is used versus 10 mEq of the combination. This is also because the greater amount of buffer results in a higher pH of the test solution in the Model over a longer period of time. For example, 20 mEq of 75% sodium bicarbonate/25% calcium carbonate maintains the pH of the test solution greater than 5.5 for 58 minutes, as compared to 10 mEq of the combination, which maintains a pH of greater than 5.5 for only 25 minutes. Similarly, 20 mEq of 50% sodium bicarbonate/50% calcium carbonate maintains the pH of the test solution greater than 5.5 for 52 minutes, as compared to 10 mEq of the combination, which maintains a pH of greater than 5.5 for only 16 minutes. And finally, 20 mEq of 25% sodium bicarbonate/75% calcium carbonate maintains the pH of the test solution greater than 5.5 for 47 minutes, as compared to 10 mEq of the combination, which maintains a pH of greater than 5.5 for only 22 minutes.

13. I further believe that the data from this study support the conclusion that treatment with a single dose of sodium bicarbonate, calcium carbonate, or a combination of the two, in an amount equal to or greater than 20 milliequivalents (mEq) per 50 mL can provide an effective dose of buffer that provides an effective window to substantially prevent or inhibit the acid degradation of a proton pump inhibitor by gastric acid. I also believe that if the pH in the stomach matches the pHs found in the Kinetic Model, it would be sufficient to preserve the bioavailability of the proton pump inhibitor administered. I further believe that the buffering agents of the present invention, when in the presence of gastric acid, could elevate the pH of the stomach sufficient to achieve adequate bioavailability of the proton pump inhibitor to effect therapeutic action.

14. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so

made are punishable by fine or imprisonment, or both, under 18 U.S.C. §101, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

November 9, 2001
Date

Joseph B. Schwartz
Joseph B. Schwartz, Ph.D.